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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROMEO, DAVID S	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/445,328	**Applicant(s)** SAMPATH ET AL.	
	Examiner David S. Romeo	**Art Unit** 1647	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 08 October 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *2,5,6,8,9,11,12,14-20,23,24,26,27,35-38 and 53-65*.
   Claim(s) withdrawn from consideration: *21,22,25 and 28-34*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/David S Romeo/
Primary Examiner, Art Unit 1647

Continuation of 11. does NOT place the application in condition for allowance because: Claims 2, 5, 6, 8, 9, 11, 12, 14, 23, 24, 26, 27, 35, 36, 37, 38, 53, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kuberasampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93).

Applicants argue that: "...there is no teaching or suggestion in the cited references or from any other source that OP-1 inhibits ICAM-I and therefore can be used to improve a standard-marker of renal function in ARF."

Applicants' arguments have been fully considered but they are not persuasive. The test for obviousness is what the combined teachings of the references would have suggested to those of ordinary skill in the art. What the Office does find Kelly to teach is that materials designed to inhibit neutrophil-endothelial interactions and prevent the accumulation of neutrophils in the kidney are useful for the treatment of acute renal failure in humans. It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to use OP-1, a material designed to inhibit neutrophil-endothelial interactions, as taught by Kuberasampath and Lefer, to prevent the accumulation of neutrophils in the kidney. That the Kelly reference exemplifies these teachings by blocking ICAM-mediated neutrophil adhesion does not diminish the generality of its teachings regarding the nature of materials that will be useful to block neutrophil adhesion.

Applicant argues that: "The cited references do not teach or suggest that any anti-adherent action on immune cells will be useful in improving a standard marker of renal function in ARF. ... one of ordinary skill in the art would not have expected that inhibition of any adherent action between immune cells and endothelial cells would improve a standard marker of renal function in ARF simply based on the effect of a single adhesion receptor molecule, ICAM-I."

Applicants' arguments have been fully considered but they are not persuasive. Kelly shows an improvement of BUN and creatinine levels, standard markers of renal function, in ICAM-deficient mice after renal ischemia. Therefore, one of ordinary skill in the art would have a reasonable expectation that blocking neutrophil-endothelial interactions would be useful in improving a standard marker of renal function.

Applicant argues that: "In fact, there are a large number of adhesion molecules that are sequentially activated during the multi-step process of transendothelial neutrophil migration (see Wagner et al., "Neutrophil Migration Mechanisms, with an Emphasis on the Pulmonary Vasculature," Pharmacological Reviews, 52:349-374 (2000) ("Wagner"), a copy of which is attached herein as Exhibit A). As illustrated in Figure 1 of Wagner, depending on the particular stage of migration, different adhesion molecules are expressed on either neutrophils or endothelial cells and each of them exhibit different activity. Thus, one of skill in the art would not have expected that the effects of inhibiting an ICAM-I mediated neutrophil-endothelial cell interaction would predict the effects of inhibiting any of the other adhesion molecules."

Applicants' arguments have been fully considered but they are not persuasive. The Wagner reference has not been entered and has not been considered. Furthermore, although there may be a large number of adhesion molecules that are sequentially activated during the multi-step process of transendothelial neutrophil migration, Kelly demonstrates that blocking a single molecule is sufficient. Furthermore, Kuberasampath and Lefer clearly demonstrate that OP-1 is effective in blocking neutrophil-endothelial cell adherence. Therefore, one of ordinary skill in the art would have a reasonable expectation that OP-1 would block neutrophil accumulation in the kidney.

Applicant argues that: "Furthermore, the cited references do not teach or suggest a nexus between OP-1 and ICAM-I. Kuberasampath discloses that OP-1 may have a role in modulating inflammatory responses that are mediated, in part, by attachments of immune cells to endothelial cells. However, there is no teaching or suggestion in Kuberasampath what OP-1 is modulating, i.e., through any specific adhesion molecule. Lefer does not remedy this deficiency. Again, there is no teaching or suggestion in Lefer what aspect of the adhesion process OP-1 is modulating on PMNs. Therefore, nothing in Kelly, Kuberasampath and Lefer teaches or suggests to the skilled worker to use OP-1 in ARF."

Applicants' arguments have been fully considered but they are not persuasive. In view of the generality of Kelly's teachings and Kuberasampath's and Lefer's teachings that OP-1 is effective in blocking neutrophil-endothelial interactions, it is not necessary for there to be a nexus between OP-1 and ICAM. One of ordinary skill in the art would have a reasonable expectation that OP-1 would block neutrophil accumulation in the kidney.

Applicants further submit that there was no teaching, suggestion or motivation in the state of the prior art to combine these references. Kuberasampath does not teach or suggest a role for OP-1 in ARF. The broad teaching of inflammation having a role in damage in the kidney would not motivate one of ordinary skill in the art to connect OP-1 with treatments for ARF such as those described in Kelly as there are many types of kidney damage that include chronic and acute diseases and only a fraction of them may lead to ARF (see Brady et al; as cited by the Examiner). Furthermore, Kuberasampath and Lefer do not teach or suggest a role for an OP/BMP renal therapeutic agent in regulating ICAM-I. The anti-adherent role of OP-1 would not motivate one of ordinary skill in the art to combine these teachings with the treatments for ARF disclosed in Kelly as OP-1 could be acting through other adhesion molecules that do not play a role in ARF.
For all the above reasons, the teaching of Kelly, Kuberasampath and Lefer do not render the claims obvious. Accordingly, applicants respectfully request this rejection be withdrawn.

Applicants' arguments have been fully considered but they are not persuasive. Applicants are broadly claiming a method of effecting an improvement in a standard marker of renal function in a mammal afflicted with ARF. Kelly teaches that blocking neutrophil-endothelial cell interactions leads to an improvement in standard markers of renal function during ARF. Kuberasampath and Lefer teach that OP-1 is effective in blocking neutrophil-endothelial interactions. It would have been obvious to one of ordinary skill in the art to use OP-1, a

material that blocks or inhibits neutrophil-endothelial interactions, to prevent the accumulation of neutrophils in the kidney. One of ordinary skill in the art would be motivated to combine these teachings in order to treat ARF in accordance with the teachings of Kelly. The argument that OP-1 could be acting through other adhesion molecules that do not play a role in ARF is mere argument. The arguments of counsel cannot take the place of evidence.

Claims 2, 15-20, 53, 54, 55 and 58-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kuberasampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93) as applied to claims 2 and 53 above, and further in view of Anderson (Chapter 275, in Harrison's Principles Of Internal Medicine, 1980) and Brady (Chapter 236, in Harrison's Principles Of Internal Medicine, 1994).

Applicants argue that: "Applicants respectfully maintain that at least for the reasons described above, nothing in Kelly, Kuberasampath and Lefer teaches or suggests the use of an OP/BMP renal therapeutic agent to improve a standard marker of renal function in ARF. Applicants submit that nothing in Anderson and Brady, either alone or in combination with any of the other documents, remedies this deficiency. Anderson discloses impaired cardiac output is a major cause of acute deterioration in renal function. Brady discloses that low cardiac output is a major cause of pre-renal acute renal failure. However, nothing in Anderson or Brady teaches or suggests a role for an OP/BMP renal therapeutic agent in regulating ICAM-I and improving a standard marker of renal function in acute renal failure (ARF). Accordingly, applicants respectfully request that the Examiner withdraw this rejection."

Applicants' arguments have been fully considered but they are not persuasive. It is the Office's position that Kelly in view of Kuberasampath and Lefer teach or suggests the use of an OP/BMP renal therapeutic agent to improve a standard marker of renal function in ARF, as discussed above.